REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

New claim 25 has been added by this amendment. Support for this claim may be found at the very least in original claim 1 and in Examples 17 and 18 of the instant application.

The Official Action states that the variable X is missing in formula (1). In the previously submitted Abstract, the X inadvertently did not print out in the formula. A corrected Abstract is submitted herewith.

Claims 1-6 and 13-24 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be rendered moot by the instant amendment.

Variable X was said to be missing from formula (1). Similar to the Abstract, the X inadvertently did not appear on the printed page for the formula (1). Formula (1) has been corrected by this amendment.

Withdrawal of this rejection is thus believed to be in order.

Claims 1-6 and 13-24 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being described by the specification. This rejection is rendered moot by the instant amendment.

The proviso language has been deleted from the claim. Withdrawal of the rejection is respectfully requested and believed to be in order.

Claims 1-6 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fukami et al, U.S. Patent No. 5,814,631. This rejection is respectfully traversed.

New claim 25 has been added. The compound of Example 148 of Fukami et al does not fall within the scope of this claim. The claim requires that the "A" benzene ring be either a 2-aminobenzenesulfonyl or a 3-aminobenzenesulfonyl. The 4-aminobenzenesulfonyl of Fukami et al would not fall within the scope of this claim. Nor would the 2- or 3-aminobenzenesulfonyl be obvious in view of the 4-aminobenzenesulfonyl of Fukami et al. Unexpected results are achieved by the claimed compounds over the 4-aminobenzenesulfonyl of Fukami et al.

In the Declaration, the solubilities of compounds described in Examples 13, 17 and 18 of the instant application and of the compound of Example 148 of Fukami et al were measured. These results are given in Table I of the Declaration. As can be seen therein, the solubilities of the compounds of the instant invention are surprisingly significantly higher than that of Example 148 of Fukami et al.

Namely, when compared with the cited compound of example 148 having 4-aminobenzenesulfonyl, the compounds having 2- and 3-aminobenzenesulfonyl (i.e., the present compounds 17 and 18) and the compound having NHCOR for R^1 (i.e., the present compound 13) have unexpectedly high solubilities in water because of the position isomer. Since one skilled in the art would have expected the position isomers to have the same properties, the properties of the claimed compounds are truly unexpected.

The solubilities of the claimed compounds are more than 11 times higher than that of Example 148 of Fukami et al. Such an increase in solubilities would not be expected, even due to the acid groups on the compounds of Examples 13, 17 and 18 of the instant application. Unexpected results are thus achieved by the instant invention.

As is well-known in the art, the oral absorbability in the oral administration depends upon the dissolving rate of the drug and the dissolving rate in the case of oral administration generally depends upon the solubility in water of the drug.

Thus, the solubilities of the present compounds 13, 17 and 18 are remarkably higher than that of the cited compound 148. Because of the difference in solubilities, when compared with the cited compound of example 148, the compounds of the instant invention as encompassed by claim 25 are expected to have a higher oral absorbability and bioavailability than those of Fukami et al. The instantly claimed compounds would thus be expected to have a higher effectiveness when orally administration. In addition, in the case of non-oral administration, since drugs should be dissolved in injection solutions, the drugs having a solubility in water are advantageous for non-oral administration as well.

In view of the marked difference in properties of the compound of example 148 of Fukami et al and the compounds of claim 25 of the instant invention, the claims of the instant invention would not be obvious in view of Fukami et al.

The §132 Declaration submitted herewith evidences that unexpected results are obtained by the instant invention. One skilled in the art would not have expected such a marked increase in solubility in water of the claimed position isomers. This increase in

solubility has many beneficial effects in terms of the use of such compounds in pharmaceutical compositions.

An unexecuted copy of the Declaration is submitted herewith. Upon receipt of the executed Declaration, a copy will be forwarded to the Patent Office. In the event that the application is reviewed prior to receipt of the executed copy, a telephone call to applicants' undersigned attorney would be appreciated.

In view of the above, withdrawal of rejection of the claims in view of Fukami et al is respectfully requested and believed to be in order.

In view of the instant amendments, at the very least claims 13-24 should be in condition for allowance. These claims were not included in the prior art rejection and the rejection under §112 is believed to be overcome. At the very least, new claim 25 should also be in condition for allowance since the compound of Fukami et al does not fall within the scope of that claim.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (650) 622-2360 so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Donna M. Meuth #39,300
for Donna M. Meuth
Registration No. 36,607

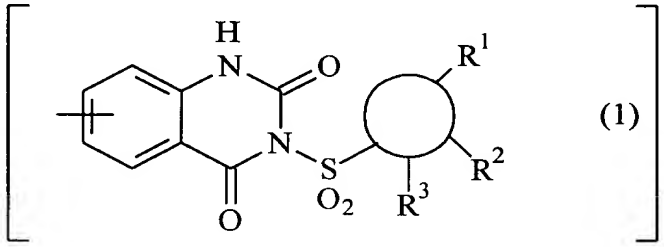
P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: April 8, 2003

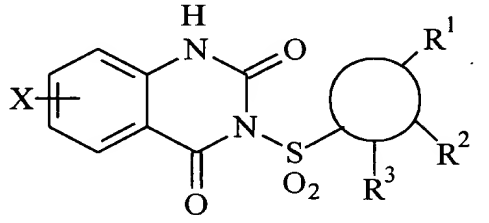
Attachment to Reply and Amendment

Marked-up Claim 1

1. (Amended) A quinazoline derivative having the following formula (1) and a pharmaceutically acceptable salt thereof:



(1)



(1)

wherein the ring A represents an aryl group:

R^1 represents (a) hydroxyl group, (b) an amino group, (c) a C_1 to C_4 lower alkylamino group which may be substituted with a COOH group, (d) a C_7 and C_{10} lower aralkylamino group which may be substituted with a COOH group, (e) an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a COOH group, (e) an amino group acylated with an aromatic ring carboxylic acid which may be

Attachment to Reply and Amendment

Marked-up Claim 1

substituted with a COOH group, (g) an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a COOH group, (h) an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a COOH group, (i) an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a COOH group, (j) an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a COOH group, (k) a C_1 to C_4 lower alkyl group substituted with a COOH group, or (l) a C_2 to C_4 lower alkenyl group which may be substituted with a COOH group;

R^2 and R^3 may be the same or different and represent (a) a hydrogen atom, (b) an unsubstituted or substituted C_1 to C_4 lower alkyl group, (c) a halogen atom, (d) a hydroxyl group, (e) a C_1 to C_4 lower alkoxyl group, (f) an amino group, (g) an unsubstituted or substituted C_1 to C_4 lower alkylamino group, (h) an unsubstituted or substituted C_1 to C_{10} aralkylamino group, (i) an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a COOH group, (j) an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a COOH group, (k) an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a COOH group, (l) an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a COOH group, (m) an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a COOH group, (n) an amino group

Attachment to Reply and Amendment

Marked-up Claim 1

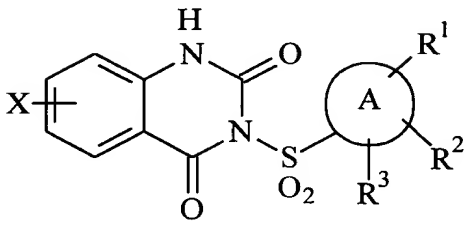
sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a COOH group, or (o) a COOH group or

when the ring A is benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, (a) a tetrahydroquinoline ring or (b) a benzoxazine ring which may be substituted with a COOH group and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X represents (a) a hydrogen atom, (b) a C_1 to C_4 lower alkyl group, (c) a C_1 to C_4 lower alkoxy group, (d) a halogen atom, (e) a hydroxyl group, (e) an amino group, or (g) a nitro group[, with the proviso that, when A is a benzene ring and R^1 is an amino group, R^2 and R^3 are not a hydrogen atom at the same time].

--ABSTRACT

A quinazoline derivative having formula (1) and a pharmaceutically acceptable salt thereof:



(1)

wherein the ring A represents an aryl group,

which derivative has a chymase inhibitory activity and suppresses the exacerbation of vascular permeability induced by chymase, and a pharmaceutical composition containing the same as an essential ingredient. These compounds are useful for treatment of allergic diseases, rheumatic diseases, and cardiac and circulatory system diseases which are due to the abnormal exacerbation of Angiotensin II production.--